Levels and Repair of Cyclobutane Pyrimidine Dimers and 6–4 Photoproducts in Skin of Sporadic Basal Cell Carcinoma Patients

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The ^{32}P-postlabeling method was applied to measure directly the levels and repair rates of specific cyclobutane pyrimidine dimers and 6–4 photoproducts in 10 basal cell carcinoma patients and 10 controls matched on age, skin type, and gender after exposure to 400 J per m^2 of solar simulating radiation on previously unexposed buttock skin. The results showed an identical level of photoproducts at 0 h after solar simulating radiation in the basal cell carcinoma group and the control group. Erythemal response correlated with the repair of cyclobutane pyrimidine dimers within 24 h in both groups, i.e., repair was faster in those with a strong erythemal reaction. The basal cell carcinoma patients showed a somewhat slower repair of photoproducts in skin compared with the controls, but the result was not significant. Photoproducts formed at the TTC sites were repaired faster than those at the TTT sites for both cyclobutane pyrimidine dimers and 6–4 photoproducts in the basal cell carcinoma group and in the controls. ***Key words: case–control study/DNA repair/erythema/ultraviolet radiation. J Invest Dermatol 115:95–99, 2000***

Basal cell carcinoma (BCC) is the commonest human cancer (Miller, 1995) and its incidence is increasing worldwide. Epidemiological studies have suggested that exposure to sunlight is the primary etiologic agent for BCC (Hunter *et al*, 1990). Host factors such as hair color and skin complexion also contribute to the risk (Hunter *et al*, 1990; Kricker *et al*, 1994). DNA is a major epidermal chromophore (Young, 1997) and there is increasing evidence that ultraviolet radiation (UVR) induced DNA damages such as cyclobutane pyrimidine dimers (CPD) and consequent mutation (e.g., p53 gene) have a direct role in the initiation of skin cancers. In humans, nucleotide excision repair (NER) is a major defense mechanism against the carcinogenic effects of UVR. Defective NER in inherited xeroderma pigmentosum patients causes a more than 1000-fold increase in risk of developing skin cancer (Kraemer *et al*, 1994). Few studies have investigated DNA repair *in situ* in human skin with BCC. Alcalay *et al* (1990), measured ultraviolet (UV) endonuclease sensitive sites and found a decreased DNA repair of CPD after 6 h of UVR in the skin of BCC patients. According to the recent studies repair of CPD in the general population was slower (half time more than 14 h) (Young *et al*, 1996; Bykov *et al*, 1999) than reported previously (less than 1 h) (Sutherland *et al*, 1980; D'Ambrosio *et al*, 1981). Thus measurement of DNA repair function at 24 h and 48 h after UVR would be relevant for the occurrence of BCC.

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Abbreviations: CPD, cyclobutane pyrimidine dimer; BCC, basal cell carcinoma; TT=T and TT=C, cyclobutane pyrimidine dimers; TT–T and TT–C, 6–4-[pyrimidine-2′-one] pyrimidine photoproduct

Both DNA photoproduct formation and DNA repair play important parts in the development of skin cancer. The formation of photoproducts can be influenced by a number of factors, such as UV wavelength (Young *et al*, 1998), skin structure (Bykov *et al*, 1998a), and constitutional factors (Xu *et al* 2000a). In this study the formation of photoproducts was investigated *in situ* in sporadic BCC patients and matched controls. In addition, the global repair rates of CPD and 6–4 photoproducts were followed in these groups. The initial level of photoproducts and their removal was also studied in terms of the erythemal response of the subjects.

MATERIALS AND METHODS

Study population This study was approved by the Medical Ethics Committee of Päijät-Häme Central Hospital, Finland. All the participants gave an informed consent concerning their participation. Ten BCC patients and 10 controls matched on age, gender and skin type were included. There were four males and six females in each group. The mean age of the BCC group was 61.0 ± 9.0 y, and 60.9 ± 10.5 y for the controls. Among the BCC cases four of them were with three BCC, one with two BCC, and five with one BCC. The classification of skin type was based on the individual anamnesis of previous skin response to sunlight.

UVR exposure and skin reaction All volunteers were exposed to 400 J per m^2 CIE (Commission Internationale de l'Éclairage; McKinlay and Diffey, 1987) erythemally weighted value of solar-simulating radiation on previously unexposed buttock skin using equipment described earlier (Snellman *et al*, 1995). This dose is equivalent to an unweighted dose of 22.14 J per cm^2 of UVA plus 0.57 J per cm^2 of UVB. The irradiance of the lamp (Philips HP 411/A) was measured (250–400 nm) prior to this study at 30 cm using an Optronic 742 spectroradiometer with Teflon diffuser as input optics, 97.5% of the irradiance being UVA and 2.5% UVB. The lamp emitted no UVR in the waveband area below 290 nm and its spectral curves mimicked the spectrum of the sun on the earth closely (summer, noontime, Helsinki latitude). The total irradiated skin area was 4 cm × 4 cm. The immediate pigment darkening (IPD) was assessed

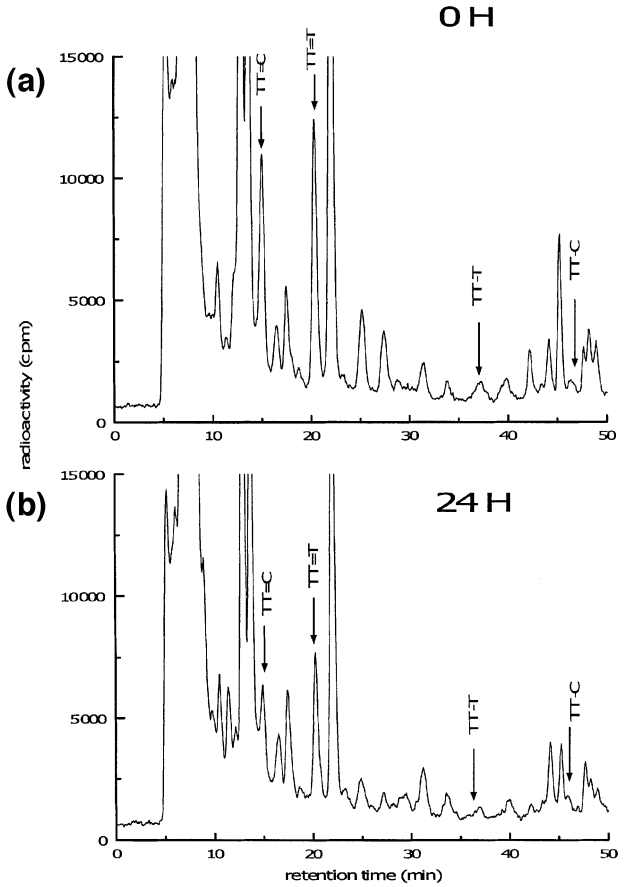

Figure 1. Identifications of CPD and 6–4 photoproducts in HPLC chromatogram. One BCC patient's profiles of the two kinds of CPD (TT = C and TT = T) and two kinds of 6–4 photoproducts (TT–T and TT–T) were shown by the arrows in the chromatograms. The UVR dose was 400 J per m^2 CIE on buttock skin as described in detail in *Materials and Methods*. (*a*) 0 h, the photoproduct levels (cpm) at 0 h after UVR; (*b*) 24 h, the photoproducts levels (cpm) at 24 h after UVR. The photoproducts were measured in 3 μg DNA each.

immediately after UVR. The classification for the degree of IPD was as follows: –, no pigmentation; +, faint pigmentation with sharp borders; ++, well-defined pigmentation. After 24 h of UVR, the 24 h erythema reaction was recorded: –, no erythema; +/–, faint erythema with indefinite borders; +, moderate erythema with sharp borders; ++, strong erythema with sharp borders. In the analysis of the relation between erythema and photoproduct levels/repair, the five subjects with no erythema (–) and faint erythema (+/–) were combined as one minimal erythemal response group (– +).

Sampling of skin biopsies After irradiation, a total of three punch skin biopsies (4 mm in diameter) were taken using lidocaine-epinephrine local anesthesia. The operation room had normal fluorescent tubes in the ceiling. The illumination was constant in all cases, i.e., the lights were on both during UV irradiation of the buttock skin and skin biopsy sampling. No extra light was used during the punch biopsy. Biopsy sampling was done within 5 min. The first sample was taken within 20 min after irradiation of UV (= 0 h), the second at 24 h and the third at 48 h. The skin biopsies were immediately put into ice, frozen, and stored at –20°C until DNA isolation.

Determination of UV-induced DNA damage in skin *in situ* Epidermis (after being separated from dermis under conditions which kept the skin biopsies frozen by precooling the mortar with liquid nitrogen) was used for DNA extraction according to a previous study (Bykov *et al*, 1999). The levels of UV-induced DNA damage (photoproduct levels) were quantified using the ^{32}P-postlabeling method, which was described elsewhere (Bykov and Hemminki, 1995; Bykov *et al*, 1999). The photoproducts were assayed as trinucleotide with an unmodified nucleotide in the 5′-side, T = C and T = T being CPD and T–C and T–T being 6–4 photoproducts. For each ^{32}P-postlabeling assay 3 μg DNA was digested and labeled. Each sample was measured twice. The undetectable level of photoproducts was assigned when the relevant fractions did not exceed the peak areas of the background noise levels two times.

After labeling, 10 μl water was added to each sample, which was then completely injected into the high performance liquid chromatography (HPLC) system for analysis. The photoproducts were detected with a Beckman ^{32}P radioisotope detector and identified by coelution with synthetic standards according to a previous method (Bykov *et al*, 1999).

Quantification of DNA damage in human skin *in situ* A series of concentrations of photoproduct standard mixture (80.2 fmol per μl TT=C, 76 fmol per μl TT=T, 79.4 fmol per μl TT–T, and 77.8 fmol per μl TT–C), in dilutions 0, 1/10, 1/5, and 1.0, were labeled in the same way as human samples. The standards were prepared as before (Bykov and Hemminki, 1995). The peak areas of photoproducts of interest in HPLC chromatogram were converted to the levels of photoproducts using the external standards above. The UV peak area of adenosine was used to determine the amount of DNA injected into the HPLC system. The levels of photoproducts were expressed as per 10^6 nucleotides.

Statistical analysis of data Data on photoproduct levels did not show a normal distribution in this study. So transformation of the data was done first to normalize them. The transformed data, however, failed to show a normal distribution. Thus, nonparametric test (Wilcoxon signed rank) was used to compare the differences of photoproduct levels and repair rate between the BCC group and the controls. In the analysis of repair rates of photoproducts, the level of photoproducts at 0 h after UVR was regarded as 100% and the repair rates at 24 h and 48 h were normalized accordingly. The significant p-value level was defined to be 0.05.

RESULTS

Identification of photoproducts The HPLC elution of two kinds of CPD (i.e., TT=C and TT=T) and two kinds of 6–4 photoproducts (i.e., TT–T and TT–C) at 0 h after UVR are shown in **Fig 1**. The identification of photoproducts was based on synthetic standards analyzed in separate HPLC runs. After 24 h post UVR, the levels of all the four photoproducts were decreased (**Fig 1**, *lower part*). In this study most samples were analyzed twice and variations between the repeat analysis were ~45% for CPD and ~57% for 6–4 photoproducts.

IPD, erythemal response had little relation with photoproduct levels at 0 h after UVR After 400 J per m^2 CIE of UVR, all subjects were examined for the IPD and for the 24 h erythemal reaction (**Table I**). There was no difference in the percentage of IPD and erythemal response between the BCC patients and the controls. No IPD took place among any of the subjects with skin types I and II. All six subjects with positive pigmentation were of skin types III and IV. No difference of pigment formation between groups/or gender was found. No relationships between IPD and photoproduct levels at 0 h, 24 h, and 48 h were found. The 400 J per m^2 CIE dose of UVR-induced erythemal response in 18 of 20 subjects (**Table I**). The two subjects who did not respond were of skin types III–IV. There was no consistent correlation between photoproduct levels and erythemal response. For example, the difference in TT = C levels at 0 h in subjects with strong erythema (++) ($18.7 \pm 10.2/10^6$ Nt) were significant ($p < 0.05$) compared with the moderate responsive subjects (+) ($12.1 \pm 7.1/10^6$ Nt). The difference, however, was not significant compared with the minimal responsive subjects (– +) ($16.7 \pm 14.7/10^6$ Nt), $p > 0.05$.

The BCC patients showed nonsignificant differences in the level and repair rate of photoproducts compared with the controls After irradiation with UV, the levels of CPD at different time points are shown in **Table I**. There were no significant differences between the BCC group and the control group in each photoproduct levels at 0 h after UVR. The levels of CPD at 0 h were about six times higher than those of the 6–4 photoproducts. The mean level of CPD (TT = C and TT = T) was $23.4/10^6$ Nt and of 6–4 photoproducts (TT–C and TT–T) was

Table I. Profiles of study population and skin reaction, photoproduct levels (per 10^6 Nt) at 0 h, 24 h, and 48 h after 400 J per m^2 of UVR[a]

Code	Age (y)	IP	24 h ery	TT=C 0 h	TT=C 24 h	TT=C 48 h	TT=T 0 h	TT=T 24 h	TT=T 48 h
BCC									
1B	48	–	++	7.4	2.6	0.5	12.5	7.4	5.5
2B	50	+	+	10.4	2.7	0.0	7.6	3.1	2.3
3B	51	–	+	5.8	3.4	0.0	8.6	2.3	3.9
4B	60	–	+	5.6	1.3	0.0	3.5	3.2	0.0
5B	68	–	+	17.5	3.7	0.0	15.2	10.1	0.0
6B	68	–	–	11.3	10.7	0.9	6.7	5.7	4.1
7B	58	–	+	12.8	5.5	1.2	8.4	6.4	4.6
8B	65	+	+–	18.4	9.2	0.5	8.0	7.6	7.1
9B	68	–	++	ND	ND	ND	13.3	10.8	6.7
10B	74	–	+	26.6	9.8	3.6	10.7	8.0	2.9
X ± SD	61.0 ± 9.0			12.8 ± 6.9	5.4 ± 3.5	1.0 ± 0.5	9.5 ± 3.5	6.5 ± 2.9	5.0 ± 2.3
Controls									
1C	49	–	+	8.6	1.2	0.0	8.1	3.4	2.4
2C	49	++	+	5.5	2.7	0.3	5.8	4.4	4.4
3C	49	–	+	13.2	3.3	2.9	15.7	8.2	6.5
4C	50	+	+–	2.7	0.7	1.0	4.6	4.2	3.0
5C	73	–	+	21.2	2.2	0.0	11.5	1.4	0.0
6C	70	+	–	10.1	3.6	0.0	10.2	6.3	4.0
7C	61	–	++	21.2	3.4	0.0	11.0	8.5	5.3
8C	67	+	+–	41.1	10.1	0.8	21.9	9.1	7.3
9C	72	–	++	27.5	5.2	0.0	18.3	12.5	0.0
10C	69	–	+	5.4	4.0	1.5	2.3	2.2	1.3
X ± SD	60.9 ± 10.5			15.6 ± 12.1	3.6 ± 2.6	0.6 ± 0.9	10.9 ± 6.2	5.2 ± 2.8	4.1 ± 2.5

[a]BCC, basal cell carcinoma; IP, immediate pigment darkening; Ery, erythema; TT=C and TT=T, cyclobutane pyrimidine dimers. The classification for the degree of IP were as follows: –, no pigmentation; +, faint pigmentation with sharp borders; ++, well-defined pigmentation. After 24 h of UVR, the 24 h erythema reaction was recorded: –, no erythema; ±, faint erythema with indefinite borders; +, faint erythema with sharp borders; ++, strong erythema with sharp borders. ND, not determined.

$4.0/10^6$ Nt in the BCC group. In the control group the mean levels of CPD and the 6–4 photoproducts were $28.7/10^6$ Nt and $5.3/10^6$ Nt, respectively. Only the difference in the TT = C level at 24 h after UVR between the BCC group and the controls was significantly different ($p < 0.05$) (**Table I**). Comparison of the repair rates for TT = T between the two groups also showed that the BCC patients tended to have poorer repair for the CPD measured (**Table I**, **Fig 2**). The differences, however, were not significant (**Fig 2**). Also, no differences were found between the two groups in the repair rate of the 6–4 photoproducts (data not shown).

Same sequence-specific repair of photoproducts in the BCC patients as in the control group A comparison of the repair efficiency at the TTC and TTT sequence, both at CPD and 6–4 photoproducts, showed that the TTC sequences were repaired much faster than the TTT sites both in the BCC and control groups (**Fig 2**). For instance, 57.4% of TT = C and 30% of TT = T were repaired in the BCC patients at 24 h after UVR ($p < 0.05$), 65.4% of TT = C and 45.5% of TT = T in the control group ($p < 0.05$). The preferred repair on the TTC sites existed also at 48 h.

Repair of CPD not 6–4 photoproducts involved in the erythemal response The analysis of DNA repair rate and erythema showed that subjects with strong erythema had higher repair rates of TT = C and TT = T at 24 h after UVR (**Fig 3**). The repair rates of TT = C and TT = T at 24 h in subjects with stronger erythema were 72.2% and 58.7%, respectively, and only 55.8% and 27.2% in the subjects with minimal erythema, respectively ($p < 0.05$). There was no significant difference between the erythemal groups at 48 h but almost all TT = C had been removed by that time (**Fig 3**). No significant relationship, however, was found between the repair of 6–4 photoproducts and the erythemal response.

DISCUSSION

The ^{32}P-postlabeling method is sensitive enough to DNA photolesions in human biopsies after UVR. Using this method our group has successfully conducted a series of studies to investigate DNA photolesions/or repair in both the general population (Bykov *et al*, 1998a, b, 1999, 2000) and people with skin diseases (Xu *et al*, 2000b). It should be noted that the reproducibility of this method can be influenced by some factors such as the amount of DNA available and the height of the HPLC peaks, which is reflected in the variation of repeat analysis of the same samples. In this study our results showed ~45% variation for CPD and ~57% variation for 6–4 photoproducts, which was similar to a previous study (Bykov *et al*, 1998a). The variation within repeat analysis of the same sample can subsequently induce part of the variations between samples. Although the interperson variation of CPD levels in **Table I** can be partly due to the method used, the interperson variation was far larger than the methodic variation. In a recent study on UV-induced DNA damage we showed that age and skin type could modulate the photoproduct levels immediately after UVR exposure (Xu *et al*, 2000a). Thus the BCC patients and cancer-free controls were matched on age, skin type, and gender in this study to minimize the effects of these factors on the assessment of UVR-induced DNA damage between the two groups. After 400 J per m^2 CIE of UVR, the BCC patients showed identical immediate photoproduct levels in the skin biopsies with the controls, both CPD and 6–4 photoproduct levels. The relative yield of 6–4 photoproducts to CPD was about 17% in each of the two groups. Using UV-endonuclease sensitive sites assay, Alcalay *et al* (1990) also found similar CPD levels in the skin immediately after irradiation in 22 BCC patients and 15 controls. These findings suggest that BCC patients have the same level of DNA photoproduct formation in skin after exposure to UVR as the general population.

The repair kinetics of photoproducts (both CPD and 6–4 photoproducts) in skin biopsies were compared both at 24 h and

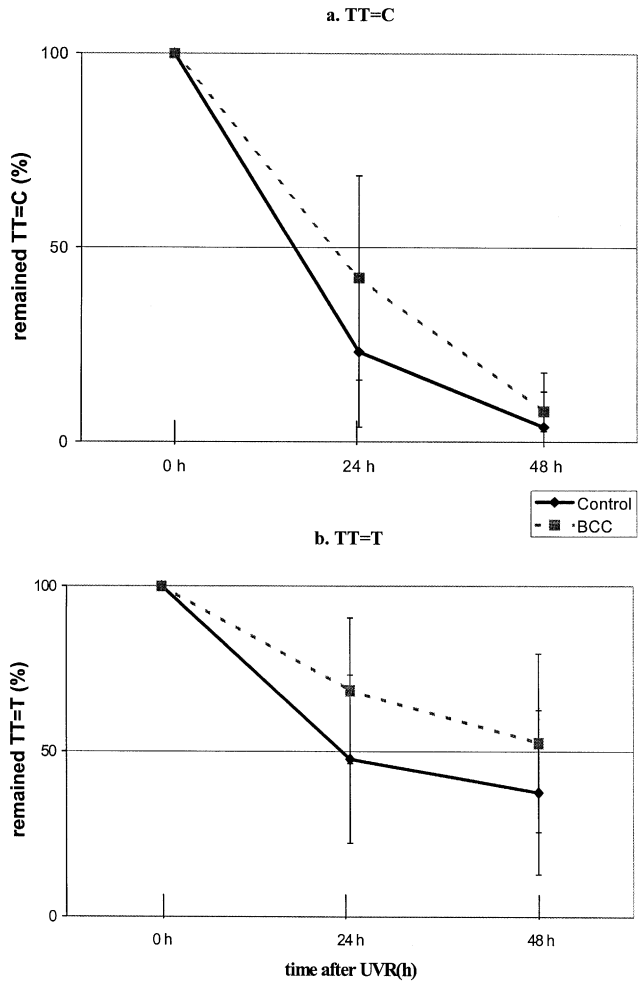

Figure 2. Repair kinetics of CPD in the BCC patients and controls. Three time points (0 h, 24 h, and 48 h) after UVR were plotted for both TT = C (*a*) and TT = T (*b*) in the BCC patients and in the control group. Each point in the figure is the mean of the unrepaired TT = C (%) or TT = T (%). The error bars are SD.

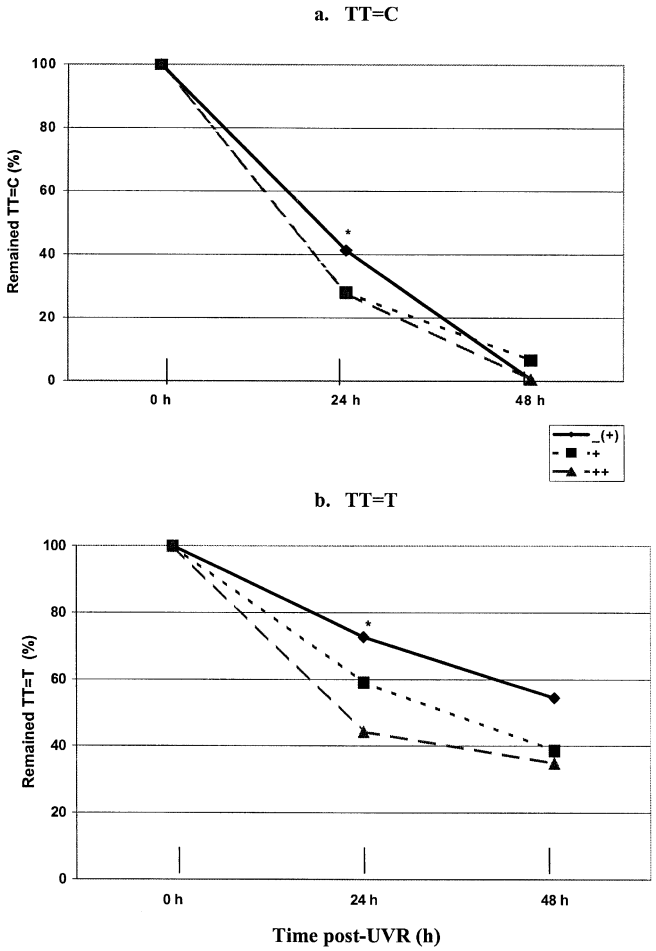

Figure 3. Higher repair of CPD in the subjects with strong erythemal response. Three time points (0 h, 24 h, and 48 h) after UVR were plotted for both TT = C (*a*) and TT = T (*b*) in the BCC patients and in the control group. *$p < 0.05$. For TT = C, minimal erythemal response group (−+) compared with both strong (++) and moderate (+) erythemal response groups at 24 h after UVR; for TT = T, minimal erythemal response group (−+) compared with strong (++) only. Each point in the figure is the mean of the unrepaired CPD (%). The SD of the means overlapped so as to make them unreadable in the figure (instead we give the ranges of SD, which were from 12.8 to 35.5%). The numbers of subjects are found in **Table I**.

48 h after UVR between the BCC patients and the controls. We found that BCC patients tended to have a lower repair for CPD measured during 24 h and 48 h after UVR in this study (**Table I**, **Fig 2**). Using an endonuclease assay, Alcalay *et al* (1990) found that only 23% of the BCC patients repaired more than 30% of the CPD after 6 h of irradiation in skin compared with 53% of the cancer-free subjects ($p < 0.05$). In this study, we measured the repair efficiency of DNA photolesions for a longer period after UVR than in an earlier study (24 h and 48 h *vs* 6 h), and our findings tended to support the results in that study (Alcalay *et al*, 1990). The difference between BCC patients and controls could be more significant if the sample size was larger in this study. In an *in vitro* study, Wei *et al* (1993) also found a decreased DNA repair capacity in peripheral blood lymphocytes in people with BCC using host cell reactivation assay. Furthermore, our study measured the specific sequence of CPD, i.e., TT=C and TT=T, so the BCC patients could have a lower repair efficiency not only of total CPD (as measured in Alcalay's study) but also of the specific CPD measured in this study. In contrast to CPD, we did not find any difference in repair for 6–4 photoproducts between the BCC patients and the controls. Because 6–4 photoproducts are repaired much faster than CPD in human skin (Young *et al*, 1996; Bykov *et al*, 1999), we could not exclude the possibility that BCC patients had a poorer repair of 6–4 photoproducts in the initial time period after UVR (i.e., less than 24 h) in our study.

It is now known that the NER process is not homogeneously distributed over the genome. The heterogeneity of NER manifests in several levels. For a variety of DNA lesions (CPD) it has been shown that NER takes place preferentially in active genes (Bohr *et al*, 1985; Bohr, 1995; Islas and Hanawalt, 1995). NER also operates even at different rates within a single gene (Tornaletti *et al*, 1993; Gao *et al*, 1994). In addition, NER has a sequence-specific repair of photoproducts in human normal skin, i.e., photoproducts formed at TTC sites are repaired faster than at TTT sites (Bykov *et al*, 1998b, 1999). In this study, the BCC patients also showed this preferable repair property of NER as the controls.

Erythema and tanning are the major acute reactions of the skin after exposure to UVR. The action spectrum for the production of DNA photoproducts in normal human skin is essentially identical to that for UV-induced erythema and tanning (Parrish *et al*, 1982; Freeman *et al*, 1989; Anders *et al*, 1995; Young *et al*, 1998). This similarity suggests that the UV induction of DNA photoproducts and/or their repair may be causally involved in these skin reactions. Furthermore, in delayed tanning melanogenesis is thought to be initiated by CPD excision fragments (Gilchrest *et al*, 1993, 1996; Eller *et al*, 1994). The relationships between photoproduct levels and IPD and erythema were investigated in our study. Because there was no significant difference of the percentage of IPD and erythema between the BCC and controls, we combined the two

groups for analysis. We did not find the relationship between photoproduct levels/or their repair rates with IPD. By contrast, we found that the subjects with a strong erythemal response had higher initial (24 h) repair rates for CPD than those with a faint erythemal response (**Fig 3**). The data suggest that fast repair of CPD could enhance the erythemal reaction. We found no difference in 6–4 photoproducts by erythemal status in contrast to a previous study using an immunohistochemical technique (Young *et al*, 1996). Both studies, however, suggest that the repair process is linked to the erythemal response.

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